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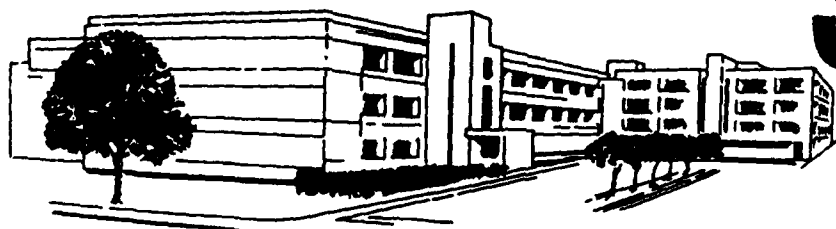
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**Resuscitation of Conscious Pigs Following
Hemorrhage: Oxygen Delivery and Demand
During Fixed-Volume Hemorrhage and
Resuscitation with 7.5% NaCl
in 6% Dextran**

**J.P. Hannon, C.E. Wade, C.A. Bossone,
M.M. Hunt, and J.A. Loveday**

DIVISION OF MILITARY TRAUMA RESEARCH

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Resuscitation of Conscious Pigs Following Hemorrhage: Oxygen Delivery and Demand During Fixed-Volume Hemorrhage and Resuscitation with 7.5% NaCl in 6% Dextran *et al.*

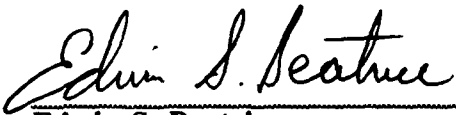
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ABSTRACT

A conscious porcine model was used to investigate the adequacy of O₂ delivery relative to O₂ demand, initially during a fixed-volume hemorrhage (37.5 ml/kg over 1 h) and subsequently after resuscitation with 7.5% NaCl/6% Dextran 70 (4 ml/kg). Hemorrhage produced a small increase in O₂ consumption, severe lactacidemia and a doubling of apparent O₂ demand. These effects were attributable to a behavioral compensation (periodic bouts of muscle activity) which presumably served to improve venous return. Despite enhanced ventilatory function, O₂ delivery was markedly reduced by hemorrhage, an effect that was due entirely to decrements in cardiac output and hemoglobin level. Resuscitation with 7.5% NaCl/6% Dextran 70 rectified the disparity between O₂ delivery and O₂ demand, primarily by suppression of demand and secondarily by improvement in delivery.

Key Words: Hemorrhage, conscious swine, resuscitation, hypertonic saline/dextran, O₂ delivery, O₂ demand.

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INTRODUCTION

The level of blood loss experienced by combat casualties and civilian accident victims is frequently so severe that death ensues in the absence of prompt and effective therapy. In most instances, this therapy is directed at preventing further blood loss and implementing resuscitation procedures that reverse the life-threatening dysfunctions associated with hemorrhagic hypotension. Efforts to improve therapy, and thereby increase the survival incidence of hemorrhage victims, have been commonly based on experimental data, but oftentimes this information is misleading because inappropriate animal models have been used to study the functional effects of hemorrhage. Ideally, an animal model should simulate the physiologic conditions found in human hemorrhage victims, particularly when the research effort is directed at the development of an improved resuscitation procedure. Ethical constraints, e.g. the extensive trauma that so often accompanies severe blood loss in humans, preclude implementing an ideal model. At a minimum, however, the hemorrhage insult should emulate the rate and magnitude of blood loss seen in humans after vascular rupture; it should occur while the animal is in a conscious state to allow full and accurate expression of the normal physiologic changes associated with blood loss; and, if enhanced survival is an endpoint for evaluating efficacy of resuscitation, the hemorrhage insult should be lethal if left untreated. We hope to demonstrate the applicability of such a model in the present communication.

In several species, including pigs [1,2], sheep [3,4], and humans [5,6], small volume resuscitation with hypertonic saline/dextran (7.5% NaCl in 6% Dextran 70) effectively reverses many of the life-threatening dysfunctions associated with hemorrhage. It also provides significant improvement in the survival of animals subjected to lethal levels of blood loss [1,2]. The beneficial effects of hypertonic saline/dextran include a return of cardiac output and arterial pressure to normal or near normal values [1-4], an increase in blood flow to vital organs [7], and a restoration of urine production [3]. These functional improvements are attributable, at least in part, to fluid mobilization from the extra- to the intravascular compartment with consequent increases in blood volume and venous return [1-4]. It is tacitly assumed that the increases in cardiac output and tissue blood flow improve oxygen delivery to previously ischemic tissues, thereby ameliorating the lethal effects of hemorrhage. The validity of this assumption, however, can be questioned, at least insofar as conscious animals are concerned. Few data are thus available on the actual levels of oxygen transport or tissue oxygen demand of conscious animals

subjected to hemorrhage, and no one has investigated these variables following resuscitation with hypertonic saline/dextran.

The foregoing information deficits precipitated the present effort. It was a component of a much larger investigation which compared the resuscitative effectiveness of 0.9% NaCl, 7.5% NaCl, 6% Dextran 70, and 7.5% NaCl/6% Dextran 70 following administration to conscious chronically-instrumented pigs that had been subjected to a lethal fixed-volume hemorrhage [1]. The effort reported here had two specific objectives. The first was to determine the effects of this hemorrhage insult on total body O_2 consumption, apparent O_2 demand and the various functional components of O_2 delivery from ambient air to the body tissues. The second objective was to determine, if possible, whether or not the resuscitative effectiveness of hypertonic saline/dextran was attributable solely to an improvement in O_2 delivery. Our data indicate that the lethality of the hemorrhage model is largely, if not entirely, due to a disparity between O_2 delivery and O_2 demand. Our data also indicate that the resuscitative effectiveness of hypertonic saline/dextran is attributable primarily to a suppression of tissue O_2 demand and secondarily to an improvement of O_2 delivery.

METHODS AND MATERIALS

Six immature (22.0 ± 1.75 kg) Yorkshire pigs were used in this investigation. Seven to 10 days before study they were splenectomized, and were chronically-instrumented with carotid and pulmonary artery catheters and an aortic sideport catheter [8], as described in detail elsewhere [1]. During this same time period, they were trained to accept a respiratory mask and physical restraint in a Pavlov sling.

On the day of study, after an overnight fast, each pig was brought into a quiet laboratory, placed in the Pavlov sling and fitted with the respiratory mask. The mask was connected by means of a 1-way Rudolph valve and 2.5 cm plastic tubing to a Horizons System metabolic apparatus for measurements of respiratory function. The pulmonary and carotid artery catheters were connected to 3-way stopcocks for blood sampling and to pressure tubing and transducers for measurements of hemodynamic function [1]. The animal was allowed to rest quietly in the sling until minimal, but stable, values for O_2 consumption were obtained; the rest interval ranged from 30 to 60 minutes. Three sets of control measurements were then taken at 10 minute intervals. Immediately thereafter, the aortic sideport catheter was opened, and a fixed-volume (37.5 ml/kg) hemorrhage schedule was initiated. Over a subsequent 60 min period, blood was removed progressively on an exponential scale such that

successive 7.5 ml/kg increments had been withdrawn after 9, 19, 31.5, 44, and 60 min. At each of these time points all measurements were repeated. Immediately after hemorrhage, the animal received a 4 ml/kg mixture of 7.5% NaCl/6% Dextran 70, injected into the pulmonary artery over a 1-min time interval. All measurements were again taken at 5, 15, 30, 60, 120, 180, and 240 minutes after the cessation of hemorrhage.

At each measurement point, a 30 ml blood sample was removed from the carotid artery and a 3 ml sample from the pulmonary artery; samples taken during the control and hemorrhage periods were included in hemorrhage volume. These samples were chilled in ice water and then partitioned for a variety of subsequent determinations. The latter included immediate measurement of O_2 content and hemoglobin concentration with an Instrumentation Laboratory Model 282 Cooximeter. Plasma lactate concentration was determined with a GEMSAEC autoanalyzer and Sigmasystem test kits. At all of the foregoing time points, expired ventilation was recorded BTPS, and O_2 consumption and CO_2 production STPD. On the basis of the foregoing measurements, cardiac output values were calculated by the Fick equation and arterial oxygen delivery as the product of arterial O_2 content and cardiac output. Apparent tissue O_2 debt was calculated from the increase in plasma lactate concentration, assuming that 1 mole of O_2 was required to oxidize 2 moles of lactate [9] and that plasma lactate concentration reflected the average concentration in total body water; a value of 640 ml/kg [10] was chosen for the latter. The sum of O_2 consumption and O_2 debt was used to estimate apparent O_2 demand of the tissues. In addition, alveolar ventilation (V_A) values were calculated by the Bohr equation:

$$V_A = \frac{(0.867)(VCO_2)}{P_aCO_2}$$

where 0.867 is a constant that converts VCO_2 from STPD to BTPS, assuming a normal porcine body temperature of 38.5C. The shunt fraction of pulmonary blood flow (Q_s) was calculated by a modification of the Fick equation:

$$\frac{Q_s}{Q_T} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_vO_2}$$

where Q_T is cardiac output, C_{c,O_2} is pulmonary end capillary O_2 content, C_{a,O_2} is arterial O_2 content, and C_{v,O_2} is mixed venous O_2 content. Temperature and Bohr factors appropriate for the oxyhemoglobin dissociation curve of porcine blood, as reported by Willford and Hill [11], were used in the calculation of C_{c,O_2} values. Finally, alveolar ventilation and cardiac output values were used to calculate ventilation-perfusion ratios, i.e. V_A/Q_T .

All data were evaluated with single factor analyses of variance adjusted for repeated measures (time). These analyses were first applied to the hemorrhage period and then to the first hour of the recovery, i.e. before any of the animals had died. Changes were considered significant when $P \leq 0.05$. In addition, mean \pm S.E.M. values were calculated for each time point during control, hemorrhage and recovery periods. At one hour and thereafter during the recovery period, two mean values were calculated for the time point that preceded death of an animal: one mean included and the other excluded the nonsurviving animal. This double calculation was directed at minimizing data distortion that might result from changes in interanimal variance associated with a reduction in group size. Representative S.E.M. values are indicated in the figures that follow.

RESULTS

The responses to hemorrhage in animals described here were not significantly different from those seen in other groups included in the overall investigation [1]. Functional changes produced by the various resuscitation solutions, however, could not be compared because of statistical constraints imposed by nonsurvival of most animals in the other groups [1]. In general, death was preceded by progressively more pronounced hypoventilation, lactic acidemia, and hypometabolism. Of the six pigs receiving 7.5% NaCl/6% Dextran 70, 4 survived the complete experimental period and 2 died, one at 70 min and the other at 190 min after resuscitation. The overall investigation did not include a non-hemorrhaged control group because previous studies [12,13] with equivalently instrumented swine models have shown that none of measured functional variables are appreciably altered as a function of time (up to 6 h).

Hemorrhage was associated with a small, progressive increase in O_2 consumption, the average values rising significantly from a control level of 6.9 ± 0.51 to 9.5 ± 0.73 ml/min/kg at the end of blood removal (Fig.1A). This effect was associated with periodic bouts of muscle activity (leg movements and stretching). During recovery following resuscitation with hypertonic saline/dextran,

O₂ consumption reverted rapidly (within 30 min) to control levels. CO₂ production (not shown) increased to a somewhat greater degree during hemorrhage than O₂ consumption, and as a consequence the respiratory exchange ratio (not shown) was increased significantly, from a control value of 0.79 ± 0.036 to a posthemorrhage value of 1.06 ± 0.094 .

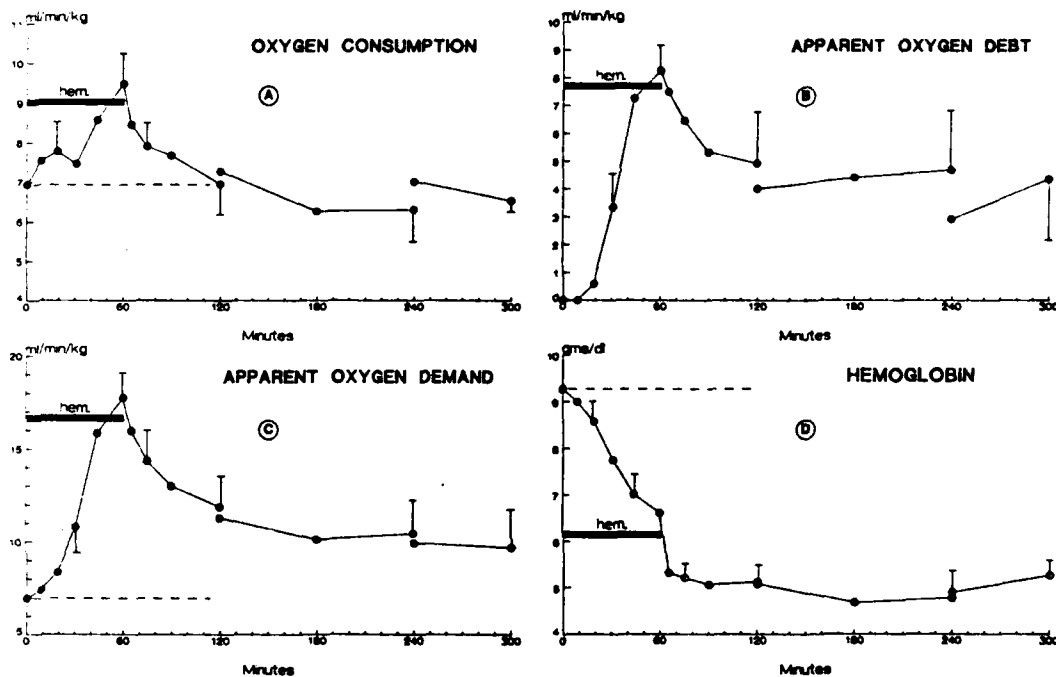


FIGURE 1. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on total body energy metabolism and hemoglobin level of conscious swine (n=6). Resuscitation (4 ml/kg) was provided immediately (over 1 min) after hemorrhage. Breaks in the plots indicate time points at which mean and S.E.M. values were calculated to include as well as exclude an animal that died shortly thereafter. Solid bar depicts the hemorrhage interval, dashed bar the control level for each variable. Significant effects ($P < 0.05$) are indicated in text.

Plasma lactate concentration (not shown), rose significantly during hemorrhage, from 0.6 ± 0.04 to 13.6 ± 1.03 mEq/L. This rise, when calculated in terms of O₂ equivalents represented an absolute O₂ debt of approximately 100 ml/kg. When calculated as a function of time, the apparent O₂ debt thus rose progressively, to 8.25 ± 0.87 ml/min/kg at the end of hemorrhage (Fig. 1B). These changes led in turn to a significant increase in apparent

tissue O_2 demand, the sum of O_2 debt and O_2 consumption, from a control level of 6.94 ± 0.51 to 15.82 ± 2.36 ml/min/kg (Fig. 1C). Resuscitation with hypertonic saline/dextran produced a significant reversion of O_2 consumption to control levels and a significant resolution of the increments in apparent O_2 debt and O_2 demand that accrued during hemorrhage.

The hemoglobin concentration of arterial blood decreased significantly during hemorrhage from 9.3 ± 0.46 to 6.6 ± 0.37 g/dl (Fig. 1D). Following administration of 7.5% NaCl/6% dextran, an abrupt further significant decrease to 5.3 ± 0.32 g/dl was observed at 5 min into the recovery period. Thereafter, hemoglobin levels remained relatively stable.

Hypermetabolism during hemorrhage was supported by increased ventilation, the expired values rising significantly from 208 ± 23.9 to 506 ± 61.3 ml/min/kg (Fig. 2A). This response was accompanied by a significant rise in alveolar ventilation from 120 ± 12.4 to 214 ± 32.2 ml/min/kg (Fig. 2B). Hyperventilation was largely, if not entirely, attributable to a significant increase in respiratory rate, from 19 ± 1.9 to 37 ± 4.2 breaths/min (Fig. 2C). Thus, tidal volume (Fig. 2D) rose only slightly during hemorrhage from 10.6 ± 0.77 to 13.8 ± 1.16 ml/min/kg, a change that was not statistically significant. Expired ventilation and alveolar ventilation decreased gradually, but significantly, following resuscitation, and the values approached control levels at 4h into the recovery period.

The combined effects of an increase in alveolar ventilation and a decrease in cardiac output (see below) led to a marked increase in the ventilation:perfusion ratio (V_A/Q_T) from 0.68 ± 0.048 to 2.15 ± 0.195 (Fig. 2E). The decrease in cardiac output also caused a significant reduction in pulmonary shunt flow (Q_s/Q_T) from 6.4 ± 0.42 to 1.4 ± 0.28 (Fig. 2F). Resuscitation with hypertonic saline/dextran produced an immediate and almost complete reversion of the V_A/Q_T ratio toward control levels. The Q_s/Q_T ratio, in contrast, was not altered significantly following resuscitation.

Hemorrhage also led to significant decrements in the O_2 content of arterial (from 11.7 ± 0.64 to 8.6 ± 0.49 ml/dl, Fig. 3A) and mixed venous (from 7.6 ± 0.63 to 0.97 ± 0.20 ml/dl, Fig. 3B) blood. The more pronounced change in the latter resulted in a significant widening of the A-V difference, from 4.0 ± 0.16 to 7.7 ± 0.41 ml/dl (Fig. 3C). Resuscitation with hypertonic saline/dextran had a significant effect on all of these variables: at the 5-min into the recovery period arterial O_2 content was further reduced to 6.8 ± 0.40 ml/dl, mixed venous O_2 content was raised to 2.5 ± 0.50 ml/dl and the A-V O_2 difference

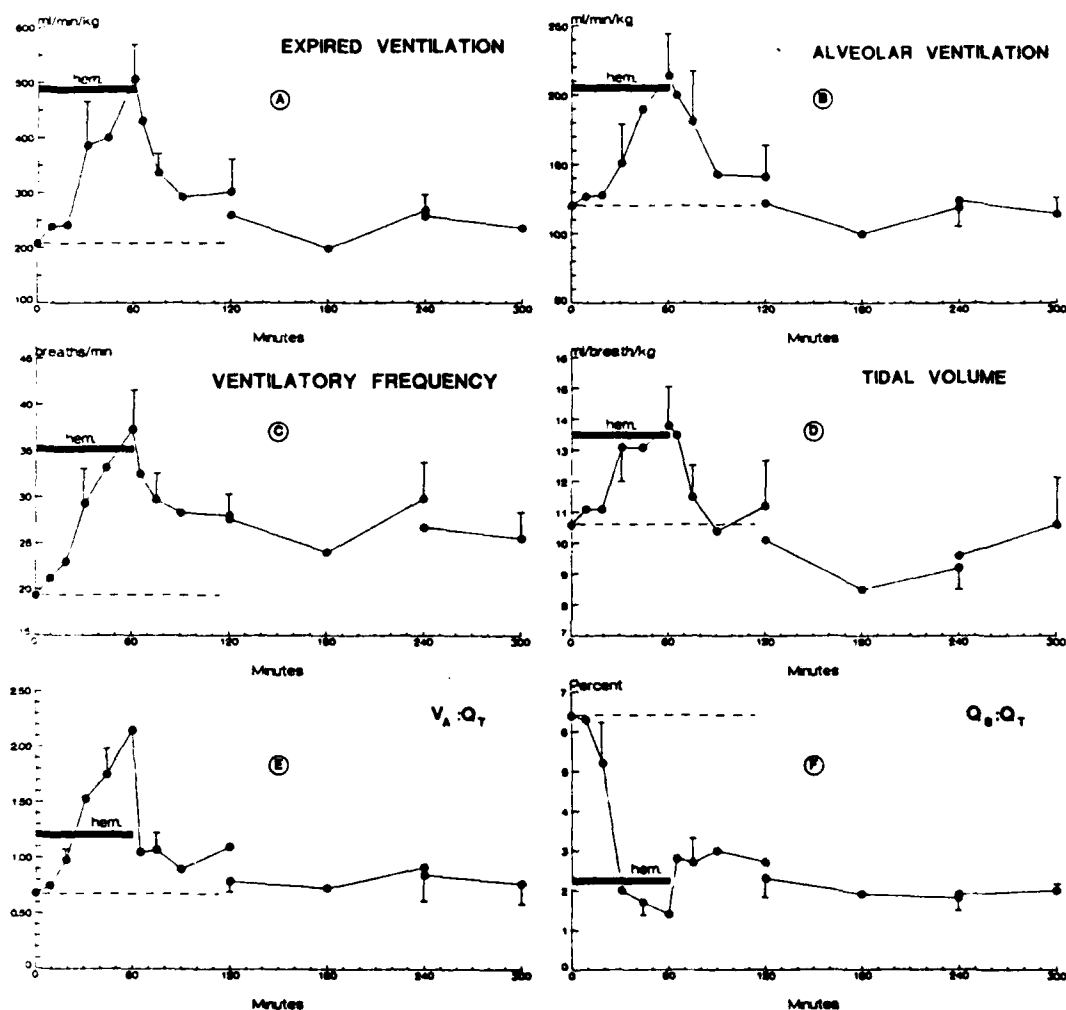


FIGURE 2. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on pulmonary functions of conscious swine. See FIGURE 1 for other experimental details.

was reduced to 4.3 ± 0.39 ml/dl. The latter value was no different than that observed under control conditions. These acute effects of hypertonic saline/dextran were maintained with little change over the subsequent course of recovery.

A significant decrease in cardiac output during hemorrhage (from 177 ± 15.6 to 98 ± 13.9 ml/min/kg, Fig. 3D) combined with the above-indicated reduction in arterial O_2 content led to a

significant reduction in arterial O_2 delivery (from 20.9 ± 2.39 to 9.3 ± 1.14 ml/min/kg, Fig. 3E). As a consequence of these changes, the ratio of O_2 delivery to apparent O_2 demand was reduced significantly from 2.96 ± 0.192 to 0.52 ± 0.055 (Fig. 3F). In short, O_2 delivery supported about one-half of the O_2 demand.

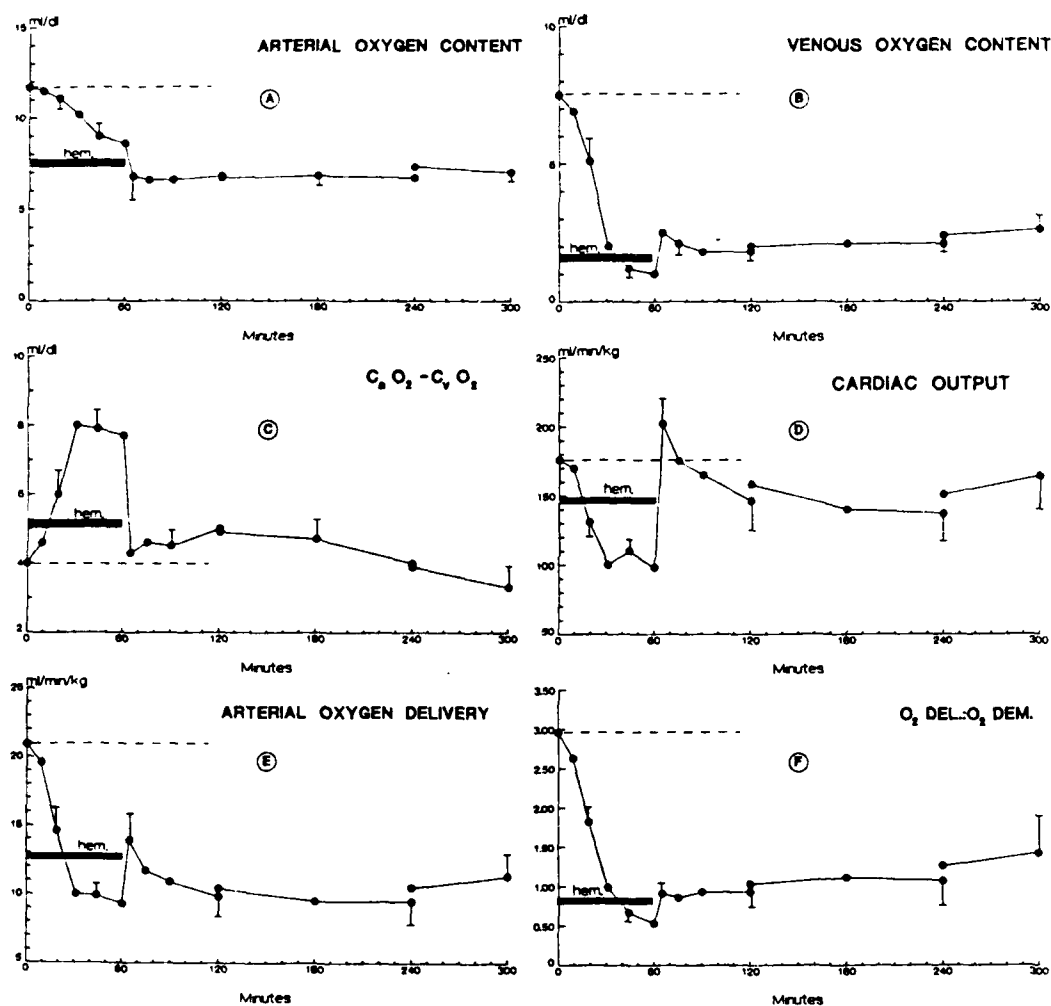


FIGURE 3. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl./6% dextran on blood oxygen delivery of conscious swine. See FIGURE 1 for other experimental details.

Resuscitation with hypertonic saline/dextran led to a marked and significant increase in cardiac output to 202 ± 19.0

ml/min/kg at the 5-min point in the recovery period. This elevation, however, was not sustained, and after 30 to 60 min the values stabilized at about 80% of the control level. Arterial O_2 delivery showed only transient, and far from complete recovery following administration of 7.5% NaCl/6% dextran. During most of the recovery period the values were essentially the same as those recorded at the end of hemorrhage. The ratio of O_2 delivery to apparent O_2 demand showed a small but significant improvement following hypertonic saline/dextran administration, an effect that was sustained over the remainder of the recovery period.

DISCUSSION

The foregoing data show that an increasing disparity between O_2 delivery and O_2 demand presents a major threat to the survival of conscious pigs subjected to severe blood loss. This disparity was not attributable to inadequate ventilatory function. Rather, oxygen delivery was compromised by reductions in both arterial O_2 content and cardiac output. The reduction in O_2 content was attributable to transcapillary refill with consequent decrements in hemoglobin concentration and blood O_2 capacity. The accompanying reduction in cardiac output resulted from a progressive decrease in blood volume with consequent decrements in venous return [1]. Apparent oxygen demand, in contrast, rose markedly during hemorrhage. It eventually exceeded O_2 delivery by a factor of at least two, as evidenced by increases in O_2 consumption, plasma lactate concentration and apparent O_2 debt. When unchecked by effective resuscitation, the disparity between O_2 delivery and O_2 demand became progressively more pronounced and eventually led to a decrease in O_2 consumption and a consistently lethal outcome [1].

On the basis of subjective evidence, it appeared that the hemorrhage-induced increase in metabolic rate was due to physical activity (leg movements, stretching, etc.), since cyclical increases in O_2 consumption coincided with periodic bouts of muscle activity. This activity, in our opinion, reflected a behavioral compensation for hemorrhage and served, presumably, to enhance venous return as blood volume was reduced. Such a compensatory response has not been reported previously, insofar as we are aware, perhaps because of constraints inherent in the animal models or procedures that were used in earlier studies of energy metabolism during hemorrhage. Indeed, most [14-22] but not all [23-25] previous reports show that hemorrhage leads to an unchanged [23-25] or reduced [14-22] O_2 consumption. It is perhaps significant that the majority of these investigations involved animals that were anesthetized, subjected to a rapid and sustained reduction in blood pressure (Wiggers procedure), or a combination of these variables. One would not expect to see

muscle activity with a consequent increase in the O_2 consumption of chemically restrained animals, and normal compensatory responses could be overwhelmed or go unobserved in conscious animals subjected to rapid blood loss or the Wiggers procedure. Only Nahas et al [26] have found metabolic increments similar to those reported here. Their results were obtained with anesthetized dogs subjected to a relatively modest, fixed-volume, hemorrhage (25 ml/kg) over a 30 min period with arterial pH maintained within 0.1 unit of 7.40. They [26] attributed the hypermetabolic effect of hemorrhage to sympathetic activation, catecholamine release, and a resultant stimulation of free fatty acid oxidation. This calorogenic effect of catecholamines was observed only in the absence of acidosis [26]. Data recorded in the present study, or obtained coincidentally, are consistent with the observations and interpretations of Nahas et al [26]. Hyperventilation and the blood buffer system effectively compensated for elevated lactic acid production (arterial pH did not change significantly) while plasma concentrations of both epinephrine and norepinephrine rose markedly [27].

It should be emphasized that our calculated values for apparent tissue O_2 demand are only approximations since they are based on lactate accumulation in plasma water and an assumed distribution of lactate in total body water. Knuttgen [9] has shown in human subjects that the O_2 equivalents of lactate, or excess lactate, accumulated during heavy physical work, closely parallel, but underestimate measured O_2 debt. Similar results might be anticipated in the present study since the plasma lactate levels reported by Knuttgen [9] were of the same order of magnitude as those recorded here for pigs. Calculations based on lactate alone underestimate total O_2 debt because a variety of other changes (depletion of body O_2 stores, creatine phosphate, etc.) contribute to an appreciable, alactacid portion of the total debt [28].

The functional mechanisms responsible for the salutary effects of hypertonic saline/dextran 70 are not totally clear, at least in terms of the factors contributing to the adequacy of O_2 delivery relative to tissue O_2 demand. On the delivery side, the improvement in cardiac output shortly after administration of hypertonic saline/dextran was consistent with the reports of others [2-4,7]. The consequent enhancement of arterial O_2 transport, however, was unimpressive, because fluid mobilization during resuscitation produced a sharp decrease in hemoglobin level and blood O_2 capacity.

Suppression of O_2 demand following hypertonic saline/dextran resuscitation appeared to be a far more important determinant of survival. It was a major factor underlying return of A-V

differences in O_2 content to normal levels, a change that indicated adequacy of O_2 delivery relative to demand. The functional changes responsible for the suppression of O_2 demand, however, were not totally resolved in the present study. It was clearly associated with a decrease in muscle activity, but other factors also may have been involved. For example, Nahas et al. [26] showed that acidosis caused a reduction in O_2 consumption during hemorrhage and attributed this effect to an inhibition of catecholamine calorogenesis. Such effects would not be inconsistent with our observations on the actions of hypertonic saline/dextran. Accordingly, other measurements made on these pigs showed a sharp reduction in arterial pH [29] and plasma catecholamine levels [27] shortly after the administration of hypertonic saline/dextran. The interactions of these and other related variables obviously need further investigation.

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